NDA 20-634/S-015, S-021, S-022
NDA 20-635/S-012, S-019, S-020

R.W. Johnson Pharmaceutical Research Institute
Attention: Robyn Keown
Senior Regulatory Associate
920 Route 202 South
P. O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Keown:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Product	NDA Number	Supplement Number	Date of Supplement	Date of Receipt
Levaquin® (levofloxacin) Tablets, 250 mg, 500 mg, 750 mg	20-634	S-015	March 9, 2000	March 10, 2000
		S-021	August 27, 2001	August 28, 2001
		S-022	October 2, 2001	October 3, 2001
Levaquin® (levofloxacin) Injection, 5 mg/mL, 25 mg/mL	20-635	S-012	March 9, 2000	March 10, 2000
		S-019	August 27, 2001	August 28, 2001
		S-020	October 2, 2001	October 3, 2001

We acknowledge receipt of your submission to each supplement dated December 11, 2001.

These supplemental new drug applications provide for the following changes to the Levaquin® pakage insert. The deleted text is noted by ~~strikethrough~~ and the added text is noted by <u>double underline</u> as follows:

1. **WARNINGS**

- A sentence was added to the last paragraph concerning tendon rupture and is now the second sentence as follows:

> <u>" Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially in the elderly."</u>

2. **PRECAUTIONS**

- In the **General** subsection, the following paragraph concerning QTc prolongation was revised to read:

> "Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. During post-marketing surveillance, ~~extremely~~ very rare cases of torsades de pointes have been reported in patients taking levofloxacin. These reports generally involved patients ~~who had other~~ with concurrent medical conditions ~~and the relationship to levofloxacin has not been established. Among drugs known to cause prolongation of the QT interval, the~~ or concomitant medications that may have been contributory. The risk of arrhythmias may be reduced by avoiding ~~use in the presence of~~ concurrent use with other drugs that prolong the QT interval including ~~hypokalemia, significant bradycardia, or concurrent treatment with~~ class Ia or class III antiarrhythmic agents; in addition, use of levofloxacin in the presence of risk factors for torsades de pointes such as hypokalemia, significant bradycardia, and cardiomyopathy should be avoided."

• In the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, the following sentences were added to the first paragraph to read:

> "Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any levofloxacin dose level and was therefore not photo-carcinogenic under conditions of this study. Dermal levofloxacin concentrations in the hairless mice ranged from 25 to 42 µg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo-carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of levofloxacin averaged approximately 11.8 µg/g at Cmax."

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revision noted below. Accordingly, these supplemental applications are approved effective on the date of this letter.

In the **PRECAUTIONS section, General** subsection please delete the word "very" as follows:

> "During post-marketing surveillance, ~~very~~ rare cases of torsades de pointes have been reported in patients taking levofloxacin."

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted December 11, 2001) and include the minor editorial revision indicated.

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 20-634/S-015, S-021, S-022, NDA 20-635/S-012, S-019, S-020." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M. D.
Acting Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht

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